DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/1/2009 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 9, 12, 18 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Fu et al (1994, Zhonghua Wai Ke Za Zhi, cited by applicants). **This rejection is maintained for reasons made of record in the Office Action dated 4/1/2009, and for reasons set forth below.**

The claims have been amended to recite systemic administration of the bacterium. Fu et al teach administration by gastric catheter (page 3), which, absent evidence to the contrary, is considered systemic administration. The claims have been further amended to recite that the tissue to be detected is "inside" of the subject as opposed to "within." These terms are considered synonymous in the context of the instant claims, and applicants have provided to means to distinguish the terms as used in the instant claims.

Response to Arguments

Applicant's arguments filed 10/1/2009 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Fu et al disclose a method for detecting bacteria, not detecting wounded or inflamed tissue; 2) Fu et al disclose administration of bacteria to rats having burn wounds in the gut caused by 30% TBSA, then follow the labeled bacteria from the injured gut tissue as it disperses.

Regarding 1), detecting bacteria at or in a wounded or inflamed tissue is an active method step recited in claim 1. Applicants assertion is also a selective reading of Fu et al, as the detection of the labeled *E. coli* within the burn wounds is found throughout Fu et al (i.e. the subeschar tissue analyzed by Fu et al is by definition is "inside" a subject: it is underneath the dead or necrotic tissue caused by the burn). This is all that is required to anticipate the broadly-worded method steps of "monitoring…the accumulation of the bacterium at or in a wounded tissue or inflamed tissue…wherein detection of accumulation indicates the location of wounded or inflamed tissue." The last step (i.e. "detection…indicates the location") is apparently a mental process performed after detection of the bacterium, which is precisely the association Fu et al make regarding the location of the labeled bacteria with the burn wounds.

Regarding 2), this is false. The term "30% TBSA" means "30% total body surface area" (TBSA is a term commonly used in the medical literature concerning burns) and thus indicates the extent of the burns, not how the burns were experimentally induced. The gut tissue of the rats of Fu et al were thus not burned as applicants insist, and the studies of Fu et al are not directed to following bacteria from wounded gut tissue as it disperses throughout the organism.

As explained, Fu et al administer the labeled bacteria to the gut, and then study areas of the body that are colonized by the bacteria.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 9, 12, 14, 16, 18 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting a cutaneous wound comprising administering a bacterial cell selected from *E. coli* and attenuated *S. typhimurium*, or attenuated *V. Cholerae* does not reasonably provide enablement for a method of detecting any given wounded or inflamed tissue inside a subject comprising administering systemically any given bacterium to a subject and detecting the accumulation of the bacterium at any given wounded or inflamed tissue inside the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of

experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims are directed to a method comprising administering a bacterium that is detectable in a subject and monitoring the subject to detect accumulation of the bacterium at wounded tissue or inflamed tissue inside the subject, whereby detection of the accumulation indicates the location of the wounded tissue or inflamed tissue. The specification states, "Any microorganism or cell is useful for the diagnostic and therapeutic uses of the present invention, provided that it replicates in the organism, is not pathogenic for the organism e.g. attenuated and, is recognized by the immune system of the organism, etc." (Paragraph bridging pages 6-7.) Thus, the claims broadly encompass practicing the claimed method using any bacterium having the capacity to accumulate at the location of any wound or any site of inflammation with sufficient specificity that the detectable accumulation of the microorganism can be used to indicate the location of a wounded or inflamed tissue.

Amount of direction provided by the inventor and existence of working examples: In support of the claimed invention, Applicant discloses that luminescent *S. typhimurim* and *V. cholera* injected into the femoral vein of nude mice and C57BU6J mice specifically accumulated at the site of cutaneous wounds. (Example 2, Figures 2-4). Given applicants arguments against certain prior art references, it is doubtful whether or not these can be considered working examples of the instantly claimed subject matter, as cutaneous wounds (such as those found in Hamblin et al) according to applicants are not to be considered "inside" a subject). It is further noted that the data presented (which consists of a single mouse for each condition) appear to show that the accumulation of bacteria depends on the strain of bacteria used, the location of the

wound and the strain of mouse. For example, the nude mouse injected with *Salmonella* exhibits accumulation of bacteria at the leg wound and ear tag (Figure 2B), the nude mouse injected with *Vibrio* exhibits accumulation only at the leg wound (Figure 3B), while the immunocompetent mouse exhibits accumulation of *Vibrio* only at the ear tag (Figure 4). Thus, the working examples demonstrate that the accumulation of any given strain of bacteria at any given wound in any given animal is highly variable and unpredictable.

The application further teaches that when inflammation was induced at a rat aortic valve by implanting a catheter near the heart valve, intravenously injected light emitting *E. coli* were found to accumulate in the heart of catheterized animals but not control animals. (Example 3 and Figure 6.)

It is noted that the application presents no data at all with respect to bacteria other than those strains listed above. With regard to the findings presented, the specification teaches, "In the experiments leading to the present invention it has been found that inflamed tissues, e.g. near implanted material, permit bacterial colonization." (Paragraph bridging pages 3-4.) The application then goes on to assert that the finding that tissues that are irritated by implanted materials are more susceptible to bacterial colonization "open the way for (a) designing multifunctional viral vectors useful for the detection of wounded or inflamed tissue based on signals like light emission or signals that can be visualized by MRI and (b) the development of bacterium- and mammalian cell-based wounded or inflamed tissue targeting systems…" (Paragraph bridging pages 4-5; emphasis added.)

Thus, the application demonstrates that some strains of bacteria will colonize areas in which foreign bodies have been implanted and seeks to claim using any bacterium having the

capacity to accumulate at the location of any wounded or inflamed tissue inside a subject with sufficient specificity that the detectable accumulation of the bacterium can be used to indicate the location of wounded or inflamed tissue. At the same time, the application acknowledges that what is demonstrated merely "opens the way for" designing vectors useful for detection of wounded or inflamed tissue and the development of bacterium-based wounded or inflamed tissue targeting systems.

With regard to accumulation of any bacterium at sites of inflammation other than wounds or tissue into which a foreign object has been introduced, e.g., an atherosclerotic lesion, the application refers to reports providing evidence that *C. Pneumonia, H. pylori,* CMV and HSV have been found in atherosclerotic plaques and speculates that intravenously administered microorganisms will penetrate into atherosclerotic plaques where they will replicate to a sufficient degree that they will be capable of indicating the presence of a plaque. (See especially the paragraph bridging pages 13-14.) However, no evidence is presented to indicate that any intravenously administered bacterium would be capable of selective accumulation within an atherosclerotic lesion such that it could actually be used to identify the location of the lesion as claimed.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there

is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In addition to the general unpredictability of the physiological arts, the unpredictability of the art related to the instant invention is clearly evidenced by the teachings of the instant application. In the paragraph bridging pages 1-2, the specification teaches (emphasis added):

> Bacteremias may arise from traumatic injuries and surgical procedures as well as from physiological functions…A potential consequence of bacteremia is colonization of susceptible sites. However, despite the occurrence of transient bacteremias, only a certain percentage of high-risk patients develop bacterial colonization of potentially susceptible sites. A number of investigators have suggested that bacteria from the blood circulation can colonize inflamed tissues in animal models and on the surface of implanted materials. The inconsistency in the pathological changes in humans following a bacteremia may also be due to the resistance of host immune system, the variability in the concentration of bacteria in the blood subsequent to different bacteremia events, and the virulence of any given bacterial strain.

Thus, the application teaches that the colonization of potentially susceptible sites by any given bacterium is variable and might be dependent on the properties of the host, the amount of bacteria present and the properties of the bacterial strain. This variability is also evidenced by the

working examples, which show that different wounds were colonized depending upon the bacterial strain injected and the mouse strain used in the experiment.

In addition, Yu et al. (2003) *Anal. Bioanal. Chem.* 377: 964-72 (of record), Applicant's own publication, provides a recent review of the art evidencing the nascent state thereof and the unpredictability of achieving the breadth of the claimed invention. With regard to bacterial cells, Yu teaches a few species of bacteria which appear to preferentially colonize cancerous tissues, but the mechanism of such colonization, while proposed to be due to various things, is not yet elucidated (pp. 966-67). Moreover, a particular mouse was found that showed a very short term accumulation of bacteria which disappeared prior to full disappearance of the bacteria in a particular mouse strain (p. 966). Further, Yu discloses that administration-type-dependent colonization is common, but there appears to be no reasoning to predict which administration will yield which colonization type (p. 966, paragraph bridging columns).

With regard to detecting areas of inflammation such as atherosclerosis, the art does not provide any guidance as to how one would detect atherosclerotic plaques as claimed. It is further noted that recent reviews of art recognized animal models of atherosclerotic disease do not mention the animal models used in the instant working examples. (See, Jawien et al. (2004) J. Physiol. Pharmacol. 55:503-517 and MacMahon et al. (2005) Curr. Drug Targets 5:433-440, of record).

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to make and use the full scope of what is presently claimed without undue experimentation. The instant application demonstrates that some strains of bacteria will colonize

areas in which foreign bodies have been implanted and seeks to claim using any bacterium or having the capacity to accumulate at the location of any wound or any site of inflammation with sufficient specificity that the detectable accumulation of the microorganism can be used to indicate the location of wounded or inflamed tissue. However, as described above, the instant application and applicant's own teachings in the non-patent literature evidence the nascent state of the relevant art even with respect to bacteria. Given this unpredictability, the skilled artisan seeking to make and use the full scope of the invention as claimed would be forced to determine experimentally which embodiments within the expansive scope of the claims would be operative (i.e., which microorganism will accumulate at any given wounded or inflamed tissue inside a subject to a degree that the accumulation can be used to indicate the location of the wound or inflamed tissue).

As stated in the application, the disclosure opens the way for designing multifunctional viral vectors useful for the detection of wounded or inflamed tissue based on signals like light emission or signals that can be visualized by MRI and the development of bacterium- and mammalian cell-based wounded or inflamed tissue targeting systems…"

"It must be remembered, however, that '[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure.' *Genentech*, 108 F.3d at 1366 (quoting *Brenner v. Manson*, 383 U.S. 519, 536 [148 USPQ 689] (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion')). Thus, while the need for some experimentation is by no means necessarily fatal, 'reasonable detail must be

provided in order to enable members of the public to understand and carry out the invention.' Id." *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003).

In view of the foregoing, the skilled artisan would not be able to practice the invention presently claimed in accordance with its full scope without having to engage in undue experimentation to extend the knowledge available in the application and the prior art such that the method could be practiced using any virus, any bacterium or any mammalian cell having the capacity to accumulate at the location of any wound or any site of inflammation with sufficient specificity that the detectable accumulation of the microorganism can be used to indicate the location of wounded or inflamed tissue as encompassed by the claims. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633